

**REMARKS**

As a result of the foregoing amendment, Claims 28, 34 and 35 have been amended.

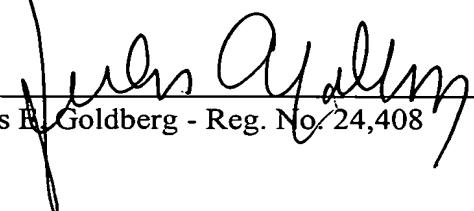
Claims 22-36 are pending in this application.

In particular, Applicants have amended Claims 28, 34 and 35 to add that the heterocyclic group for R<sup>5</sup> may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino. Support for this amendment can be found in a specification at page 17, Table 1-4. Applicants have also attached hereto a marked-up copy of Claims 28, 34 and 35 showing the changes with brackets and underlining. No new matter has been added.

In addition, further to 37 C.F.R. § 1.56, Applicants respectfully submit that Claims 22-31 and 36 were owned by Yutaka Nomura and Toshihiro Takahashi at the time when the invention covered by these claims was made, Claims 32 and 34 were owned by Yutaka Nomura, Toshihiro Takahashi and Yasushi Yoshino at the time when the invention covered by these claims was made and Claims 33 and 35 were owned by Yutaka Nomura, Toshihiro Takahashi and Koichiro Nishioka at the time when the invention covered by these claims was made.

In view of the foregoing, it is submitted that this application is now in condition for allowance and favorable reconsideration and prompt notice of allowance are earnestly solicited.

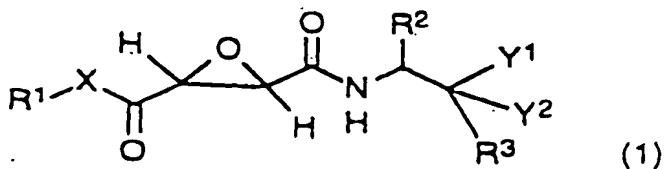
Respectfully submitted,  
REED SMITH, LLP

By:   
Jules R. Goldberg - Reg. No. 24,408

March 22, 2001  
375 Park Avenue, 17<sup>th</sup> Floor  
New York, NY 10152  
Tel. (212) 521-5400  
JEG/SRP

MARKED-UP COPY OF CLAIMS 28, 34 AND 35

28. An epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt:



wherein

R<sup>1</sup> represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R<sup>2</sup> represents an isobutyl group or an isopropyl group;

R<sup>3</sup> represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or -NR<sup>4</sup>- in which R<sup>4</sup> is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group comprising a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y<sup>1</sup> represents OR<sup>5</sup> is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acyl group having 2 to 20 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group

comprising a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

$Y^2$  represents a hydrogen atom;

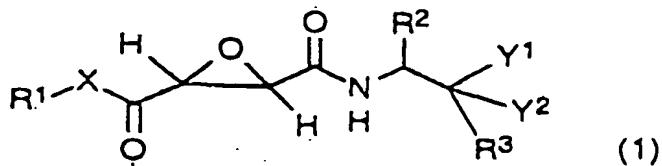
provided that the alkyl group for  $R^5$  may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino[, and];

provided that the aryl group for  $R^1$ ,  $R^3$  and  $R^5$  may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino[.]; and

provided that the heterocyclic group for  $R^5$  may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino.

34. A method for treating bone diseases which comprises injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its

physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of 0.1 mg/day to 1 g/day in the case of oral administration:



wherein

R<sup>1</sup> represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R<sup>2</sup> represents an isobutyl group or an isopropyl group;

R<sup>3</sup> represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or -NR<sup>4</sup>- in which R<sup>4</sup> is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group comprising a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y<sup>1</sup> represents OR<sup>5</sup> is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acyl group having 2 to 20 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group comprising a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y<sup>2</sup> represents a hydrogen atom;

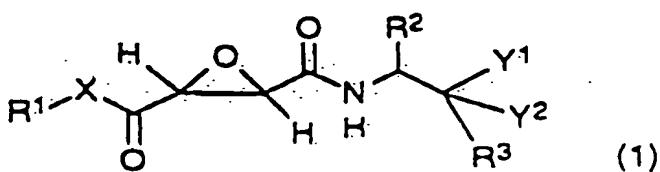
provided that the alkyl group for R<sup>5</sup> may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino[, and];

provided that the aryl group for R<sup>1</sup>, R<sup>3</sup> and R<sup>5</sup> may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino[.]; and

provided that the heterocyclic group for R<sup>5</sup> may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino.

35. A method for treating arthritis which comprises injecting or orally administering into a patient an epoxysuccinamide derivative having the following formula (1) and its physiologically acceptable salt in an amount of 0.01 to 100 mg/day in the case of injection or in an amount of

0.1 mg/day to 1 g/day in the case of oral administration:



wherein

R<sup>1</sup> represents a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, an alkynyl group having 2 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, or an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

R<sup>2</sup> represents an isobutyl group or an isopropyl group;

R<sup>3</sup> represents a hydrogen atom or an aryl group having 6 to 20 carbon atoms;

X represents -O- or -NR<sup>4</sup>- in which R<sup>4</sup> is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group comprising a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms;

Y<sup>1</sup> represents OR<sup>5</sup> is a hydrogen atom, an alkyl group having 1 to 10 carbon atoms, an aryl group having 6 to 20 carbon atoms, an aralkyl group comprising an aryl group having 6 to 20 carbon atoms and an alkyl group having 1 to 6 carbon atoms, an acyl group having 2 to 20 carbon atoms, a heterocyclic group having 3 to 12 carbon atoms, or a heterocyclic-alkyl group comprising a heterocyclic group having 3 to 12 carbon atoms and an alkyl group having 1 to 6 carbon atoms; and

Y<sup>2</sup> represents a hydrogen atom;

provided that the alkyl group for R<sup>5</sup> may have one or more substituents selected from the group consisting of hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, and guanidino[, and];

provided that the aryl group for R<sup>1</sup>, R<sup>3</sup> and R<sup>5</sup> may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino[.]; and

provided that the heterocyclic group for R<sup>5</sup> may have one or more substituents selected from the group consisting of alkyl having 1-6 carbon atoms, hydroxyl, amino, alkylamino having 1-6 carbon atoms, dialkylamino having 2-12 carbon atoms in total, alkoxy having 1-6 carbon atoms, halogen, haloalkyl having 1-6 carbon atoms, cyano, nitro, carboxyl, alkoxycarbonyl having 2-7 carbon atoms, carbamoyl, alkylaminocarbonyl having 2-7 carbon atoms, dialkylaminocarbonyl having 3-13 carbon atoms in total, amidino, and guanidino.